Influenza Pandemics of the 20th Century

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Influenza: Epidemics and Pandemics

- **Influenza is an annual cause of significant morbidity and mortality: epidemics recognized in temperate areas for many years**
- **Unpredictably and at irregular intervals, pandemics associated with increased mortality occur**
- **Attack rates approach 40-50% in some populations**
- **Criteria for a pandemic influenza virus:**
  - **novel influenza A strain**
 - **little or no immunity in population**

Antigenic Change

- **Antigenic 'drift' occurs in HA and NA**
  - **Associated with seasonal epidemics**
  - **Continual development of new strains secondary to genetic mutations**
  - **A viruses >> B viruses**
- **Antigenic 'shift' occurs in HA and NA**
  - **Associated with pandemics**
  - **Appearance of novel influenza A viruses bearing new HA or HA & NA**

Influenza Viruses Infect Several Animal Species

- **All influenza A subtypes recognized to date are found in wild birds**
  - **Fecal transmission common among wild birds**
  - **Usually, infections occur without illness**
- **Other animal species**
  - **Domestic poultry (chickens, ducks and quail)**
  - **Humans, swine, horses, seals, whales**
- **Humans usually infected by human influenza viruses**

Circulation of Influenza A viruses in humans in the last century
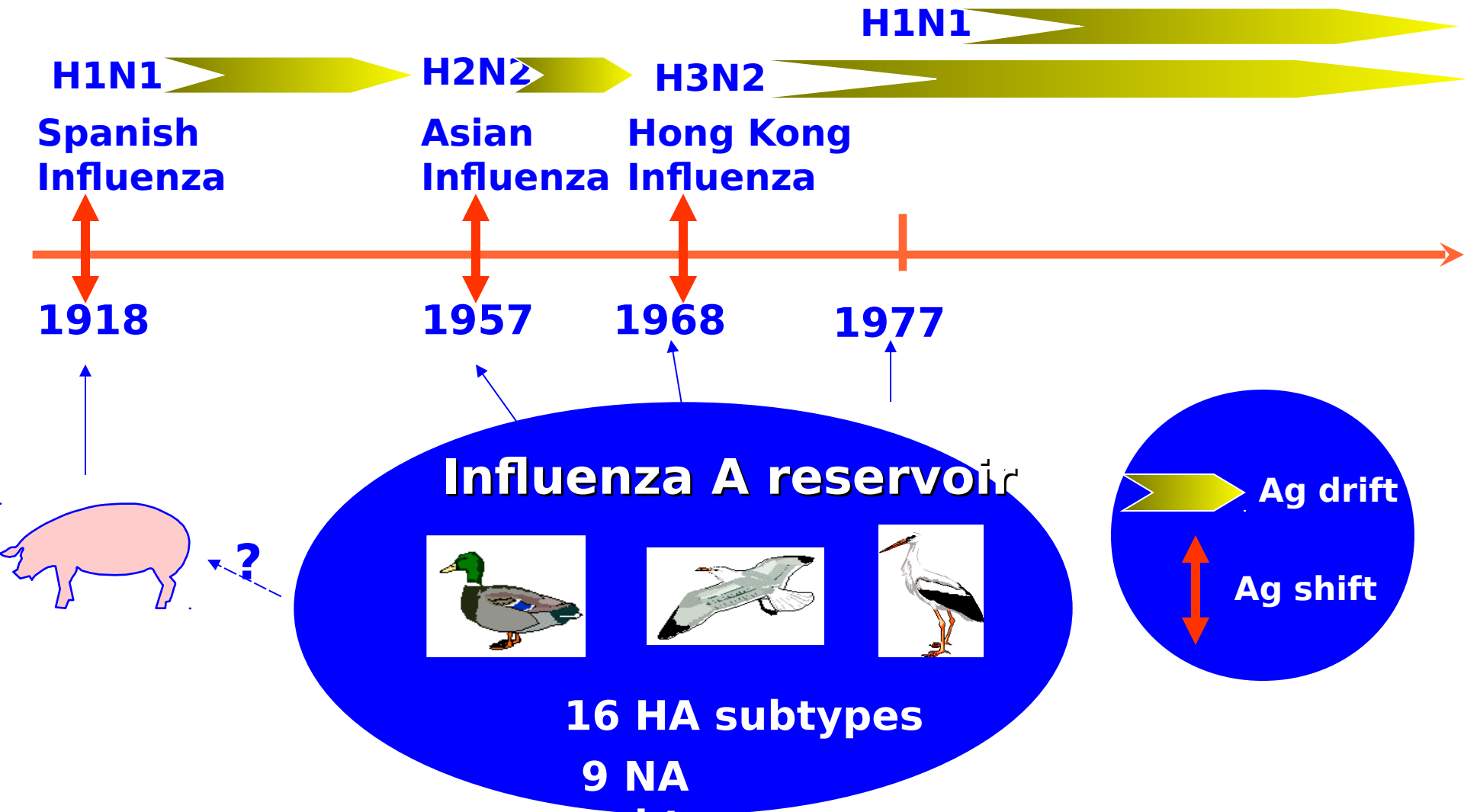
Pandemics and Pandemic Threats of the 20th Century

- 1918-19 "Spanish flu"   H1N1
- 1957 "Asian flu"   H2N2
- 1968 "Hong Kong flu"   H3N2
- 1976 "Swine flu" episode H1N1
- 1977 "Russian flu"   H1N1
- 1997 "Bird flu" in HK   H5N1
- 1999 "Bird flu" in HK   H9N2
- 2003 "Bird flu" in Netherlands H7N7
- 2004 "Bird flu" in SE Asia   H5N1

Selected patterns among 20th century pandemics

- Geographic spread
- Mortality (vital statistics, surveys) by age group
- Attack rates and pneumonia rates by age group
- Morbidity & mortality by area
- Timelines for vaccine development

Impact of Influenza Pandemics

1918-19 Spanish Flu (H1N1)
- 20 to 40 million deaths worldwide
- At least 550,000 US deaths (only 80% of pop. included in vital statistics data)
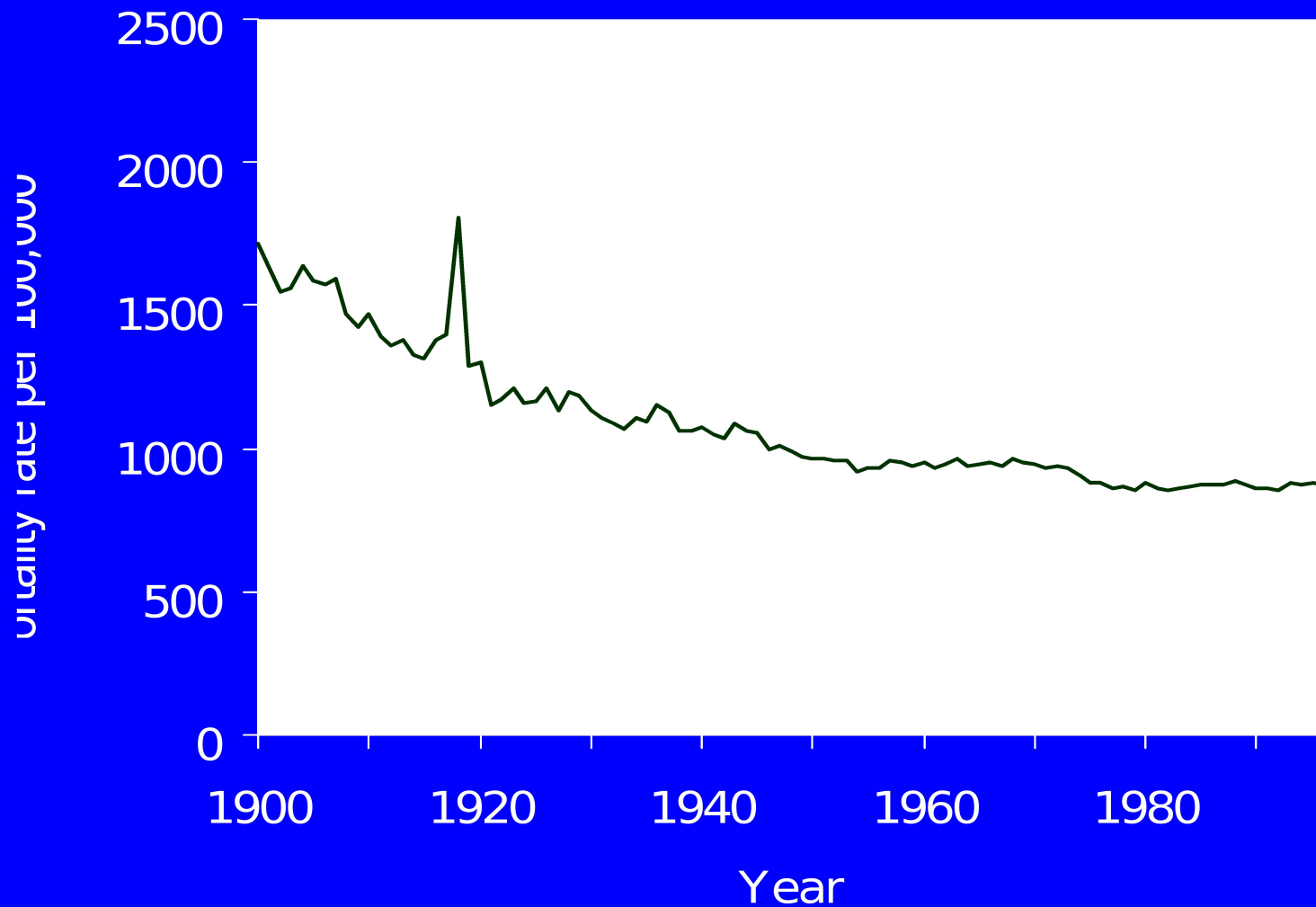
1957-58 Asian Flu (H2N2)
- ~70,000 US deaths
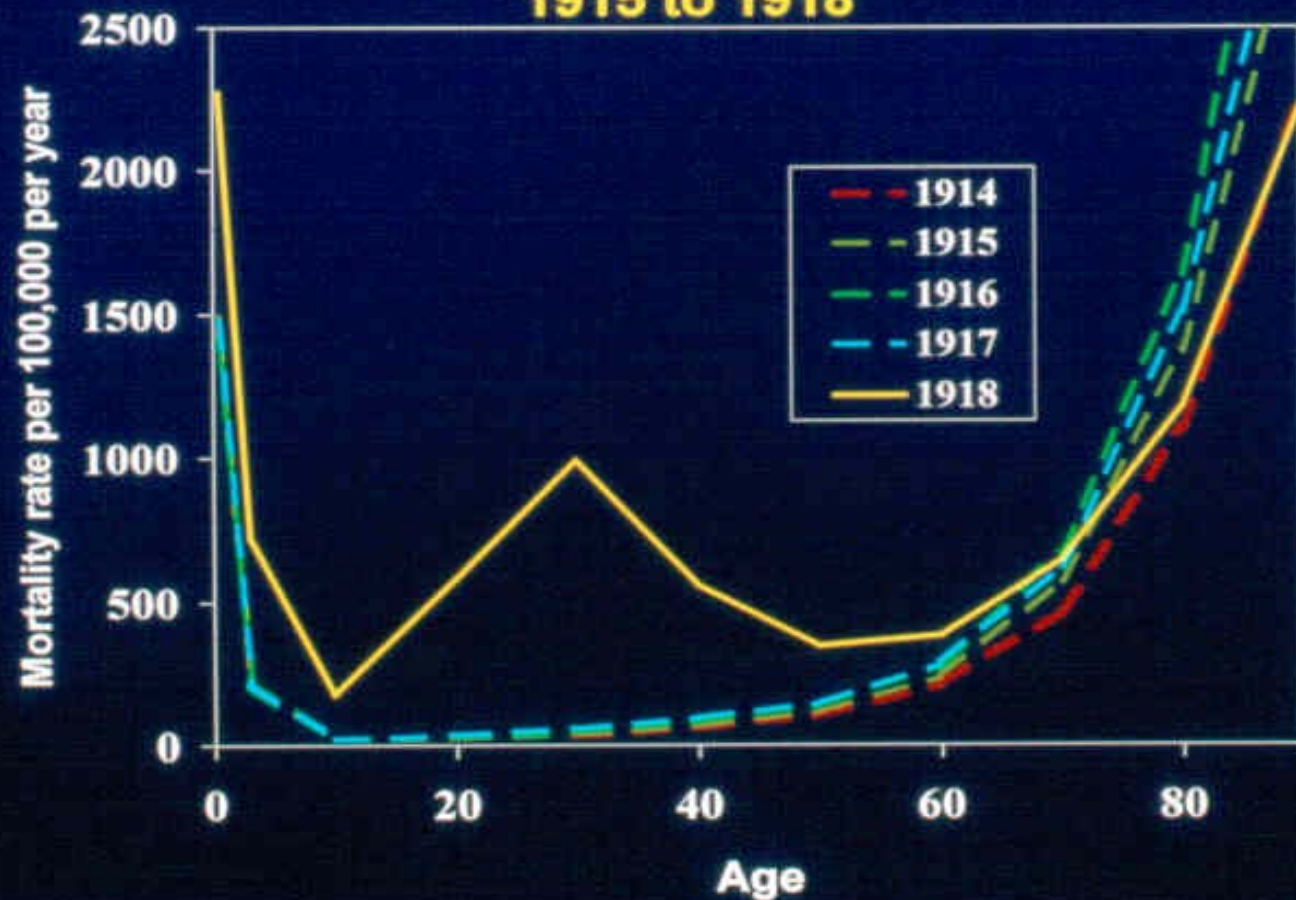
1968-69 Hong Kong Flu (H3N2)
- ~34,000 US deaths

Current interpandemic influenza
- ~36,000 US deaths
- >200,000 hospitalizations

20th century mortality rates: 1918-1919
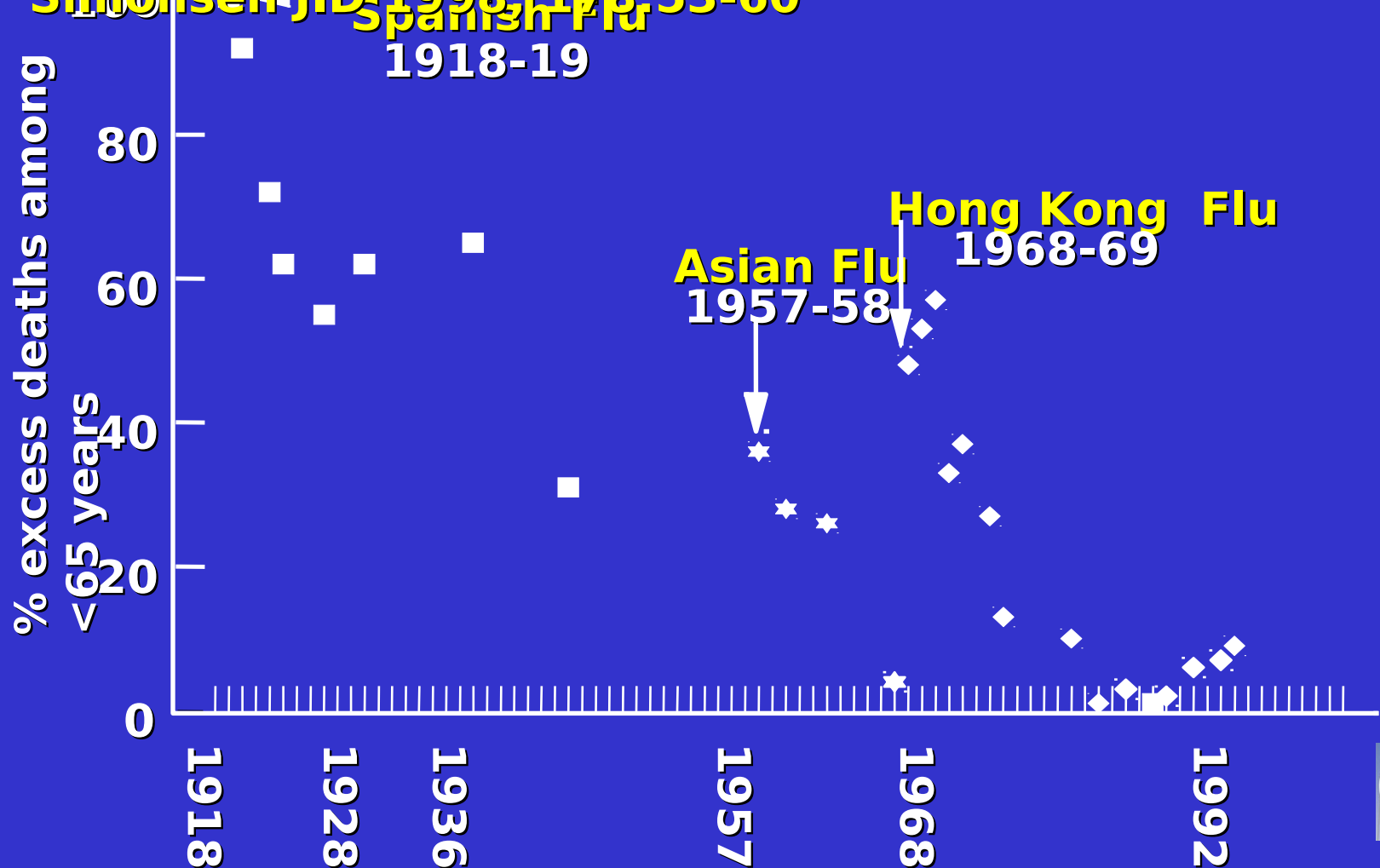
Age-specific pneumonia and influenza mortality, 1915 to 1918

Excess Pneumonia & Influenza Deaths in Persons <65 years during and after Pandemics (from vital statistics data)

Simonsen JID 1998; 178:53-60

Spanish Flu 1918-19

Hong Kong Flu 1968-69

Asian Flu 1957-58

% excess deaths among <65 years

CDC

Excess mortality among those <65 in the 20th century

- **1918: >90% of excess deaths occurred among those aged <65**
- **1936-37: about 60% of excess deaths in <65**
- **1943-44: only 30% in <65**
- **1957-58: 36% of excess deaths in <65**
- **1967-68 (end of H2N2 circulation): only 4% in <65**
- **1968-69: ~40% of excess mortality in <65**
- **Since 1992, <10% of excess deaths**

Total number of persons age 65 or older, by age group, 1900 to 2050, in millions
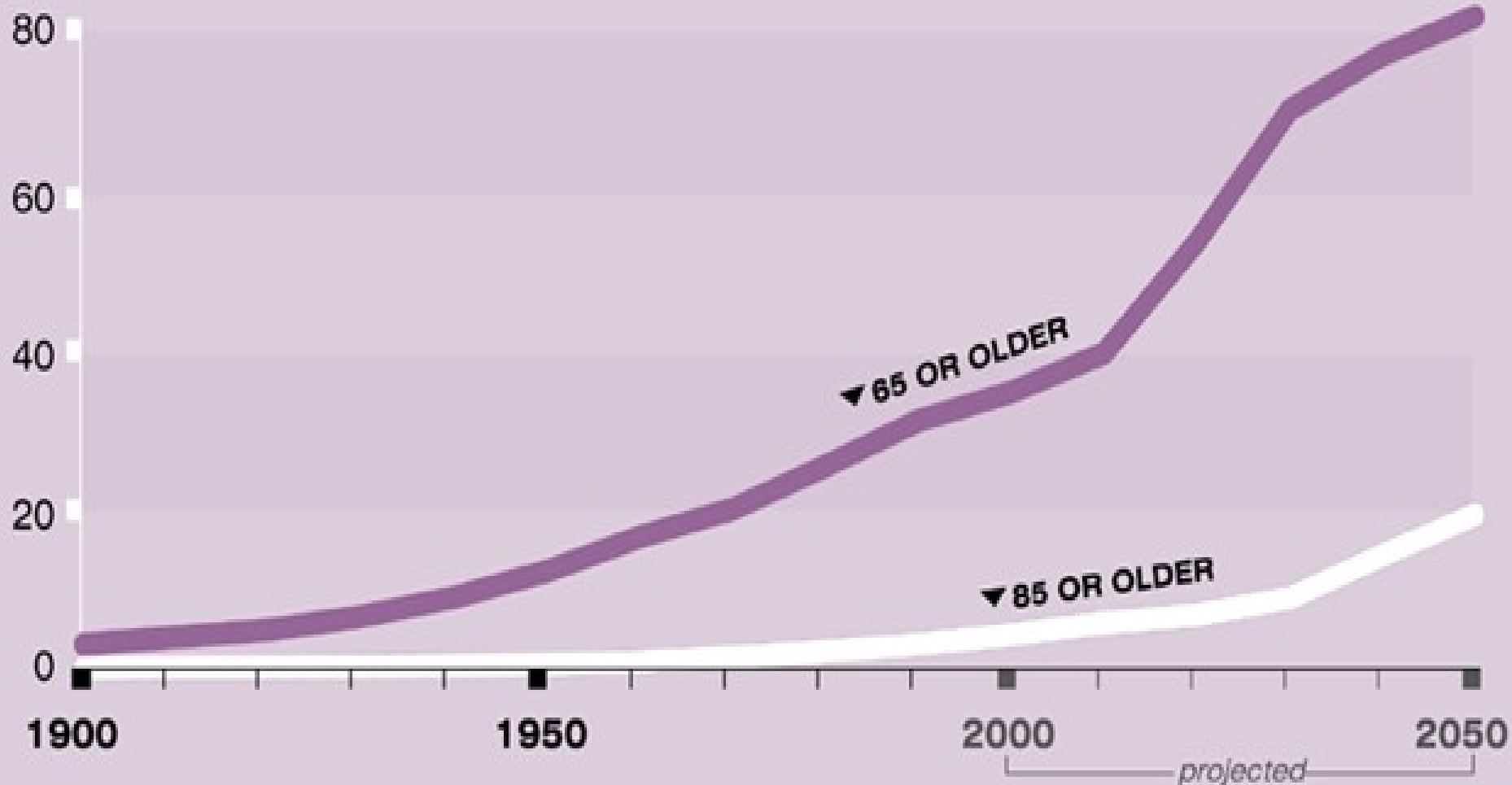
Note: Data for the years 2000 to 2050 are middle-series projections of the population.
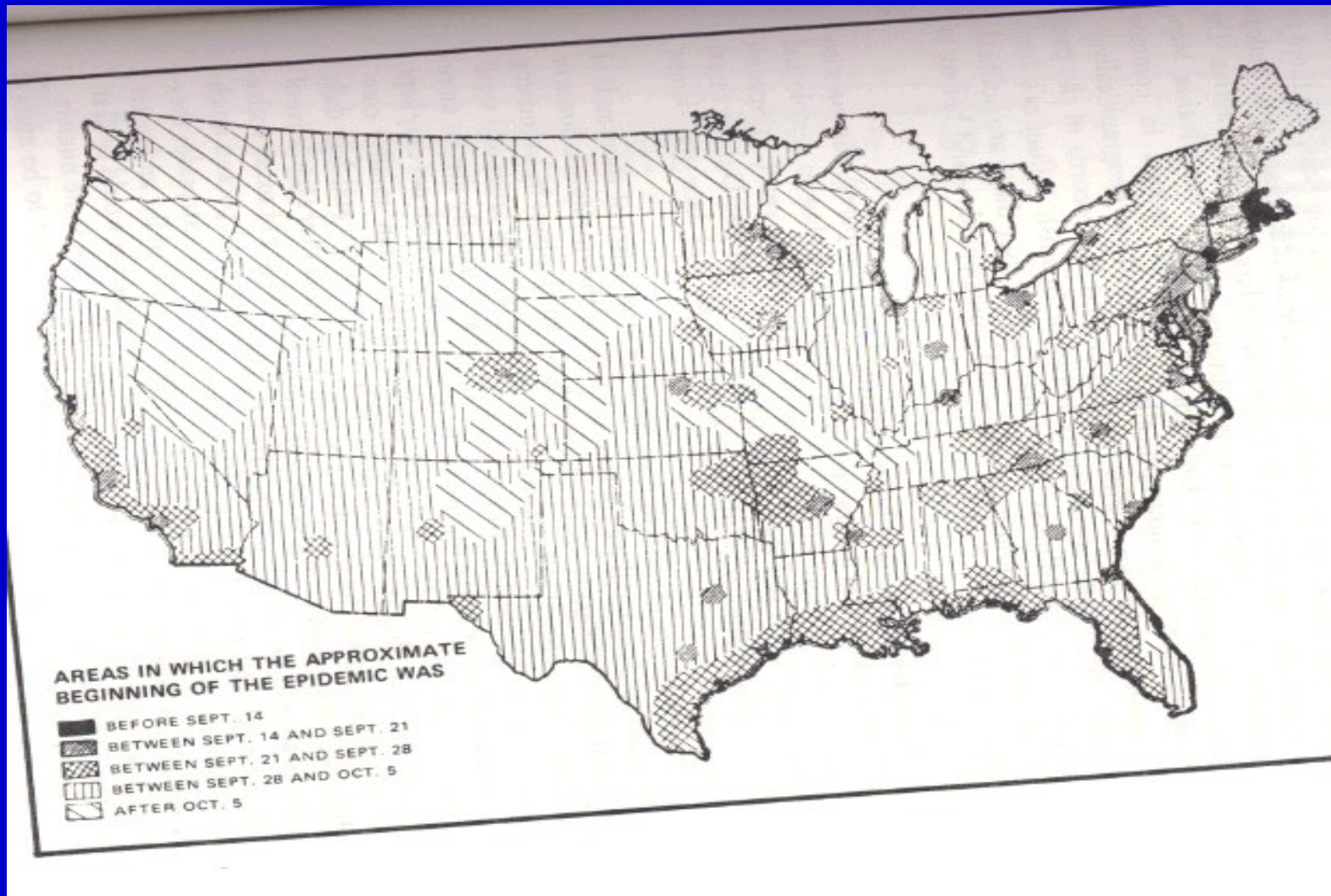
Reference population: These data refer to the resident population.

Source: U.S. Census Bureau, Decennial Census Data and Population Projections.
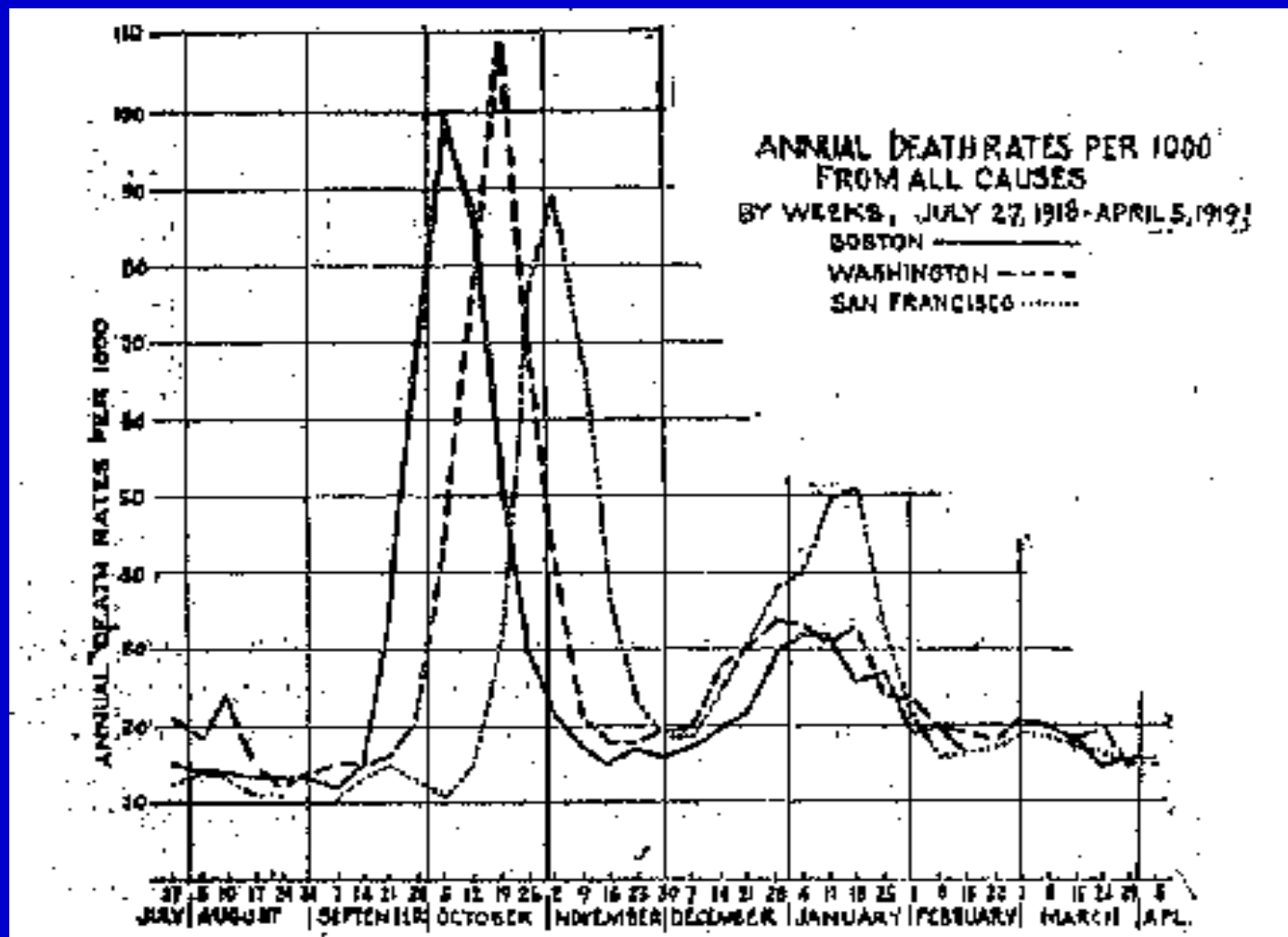
Worldwide impact of 1918 influenza pandemic

- **Patterson & Pye estimated 30 million deaths worldwide (Bull Hist Med 1991)**

- **Mortality rates by region**
  - **5 per 1000 in Europe and North America**
  - **9 per 1000 in Central & South America**
  - **15 per 1000 in Africa**
  - **20-34 per 1000 in Asia, with highest rates in India (estimated 12.5-17 M deaths in India)**

1ˢᵗ wave: Sept to Oct 1918

AREAS IN WHICH THE APPROXIMATE
BEGINNING OF THE EPIDEMIC WAS

- BEFORE SEPT. 14
- BETWEEN SEPT. 14 AND SEPT. 21
- BETWEEN SEPT. 21 AND SEPT. 28
- BETWEEN SEPT. 28 AND OCT. 5
- AFTER OCT. 5

Death rates in 3 cities: 1st & 2nd waves

US mortality during 1918 pandemic using Registration Area data

- **Overall excess pneumonia and influenza mortality was 5.3 per 1000**
- **In states included (no TX, FL, GA etc)**
  - **Low – 3.6 per 1000 in Wisconsin**
  - **High – 7.5 per 1000 in Montana**
- **In 45 cities with >100,000 residents**
  - **Low – Grand Rapids: 1.9 per 1000**
 - **High – Pittsburgh: 10.3 per 1000**

WH Frost. The epidemiology of influenza. Public Health Reports 1919;34:1823-36

"...there are notably wide differences in the mortality rates of individual cities..., even between cities close together, differences which are not as yet explained on the basis of climate, density of population, character of preventive measures exercised, or any other determined environmental factor"

USPHS surveys of 1918 pandemic

- **House-to-house surveys were conducted in 11 cities in 1919; N ~ 113,000**
- **Overall attack rate 280 per 1000**
  - **Louisville: 150 per 1000**
  - **San Antonio: 530 per 1000 (3.5 x higher)**
- **Attack rates consistently highest among those aged 5-14 years**
  - **Fell off gradually in younger and older**
 - **Lowest rate among those aged 75+**

USPHS survey: case rates
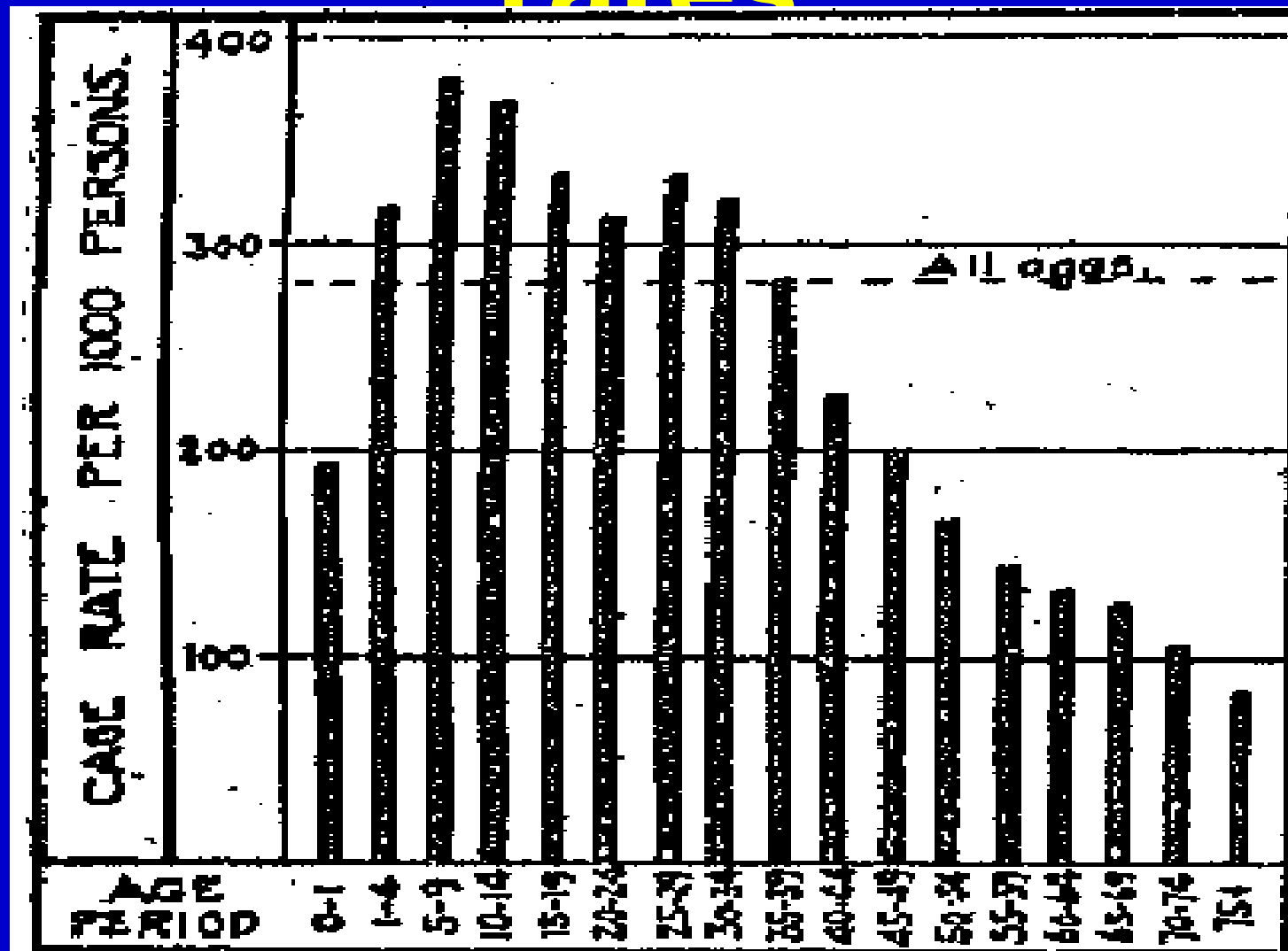
USPHS surveys: pneumonia rates

- **Pneumonia rates showed little correlation with attack rates**
- **Pneumonia rates also varied by city**
  - **from 5.3 per 1000 in Spartanburg**
  - **to 24.6 in rural Maryland (4.6 x higher)**
- **Death rates paralleled pneumonia rates**
  - **1.9 per 1000 in Spartanburg**
  - **6.8 per 1000 in Maryland (3.5 x higher)**

USPHS surveys: fatality rate

FATALITY RATE PER 100 CASES OF INFLUENZA AND PNEUMONIA (ALL FORMS)
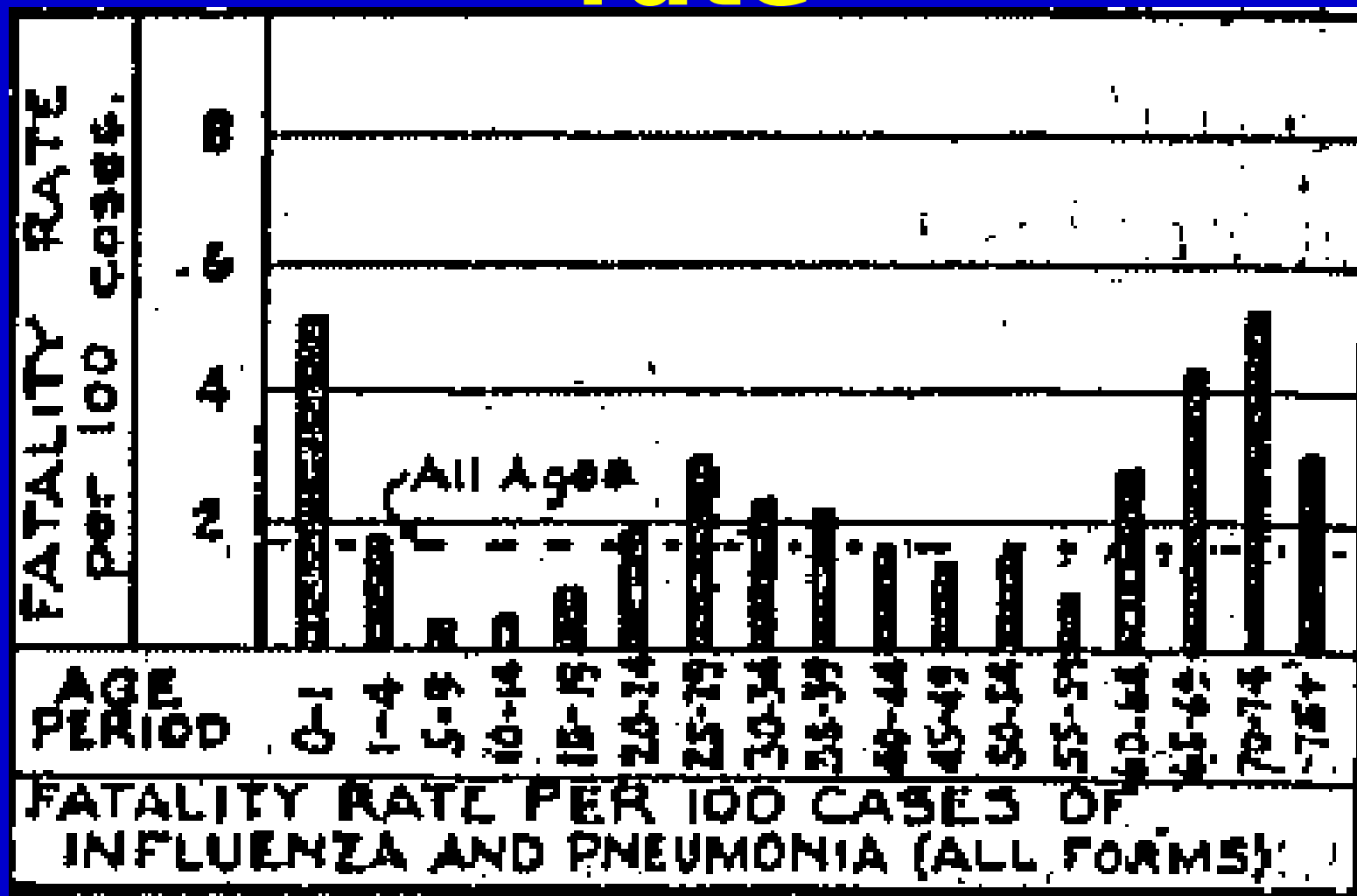
USPHS surveys: death rates
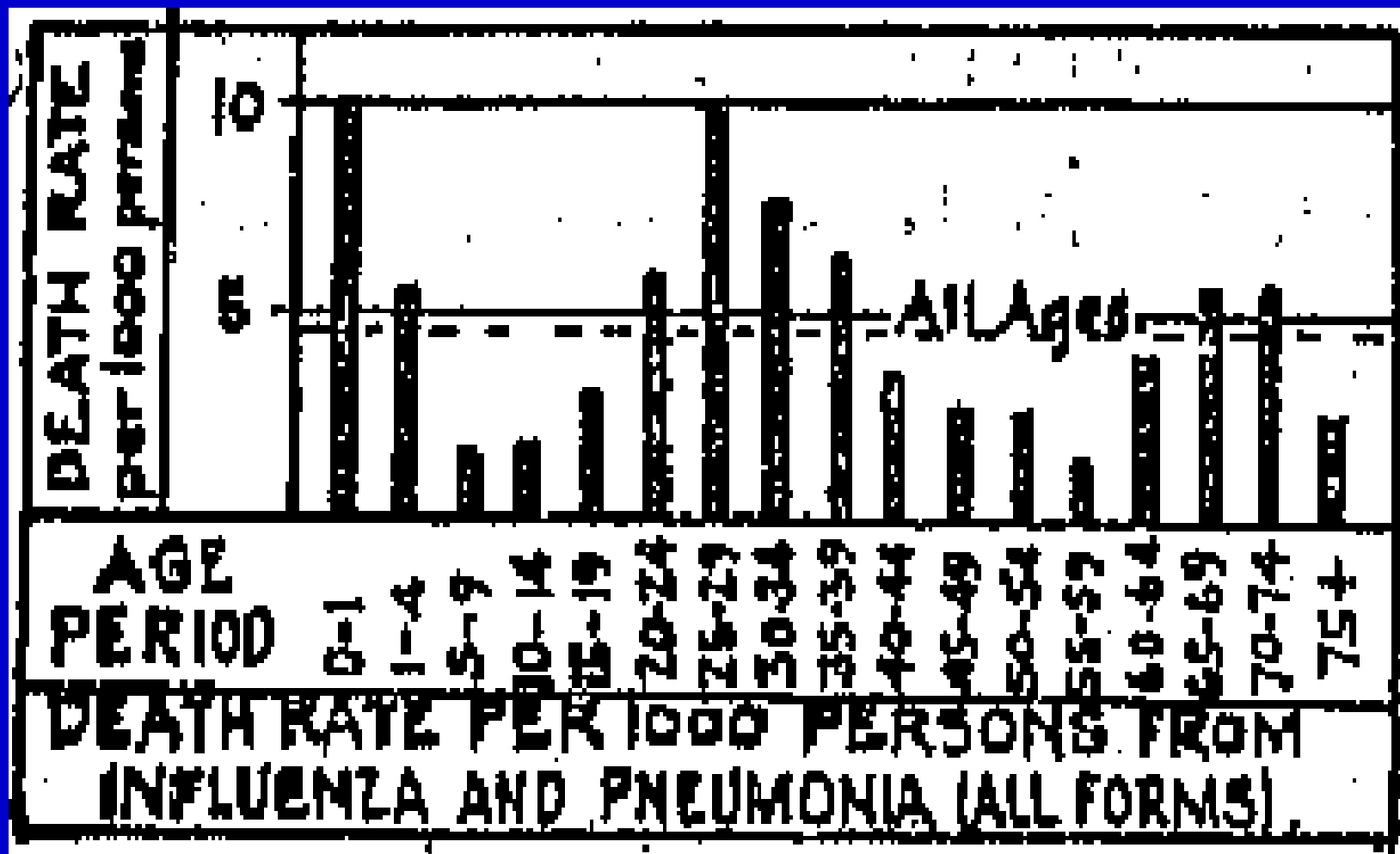
SPREAD OF H2N2 INFLUENZA IN 1957
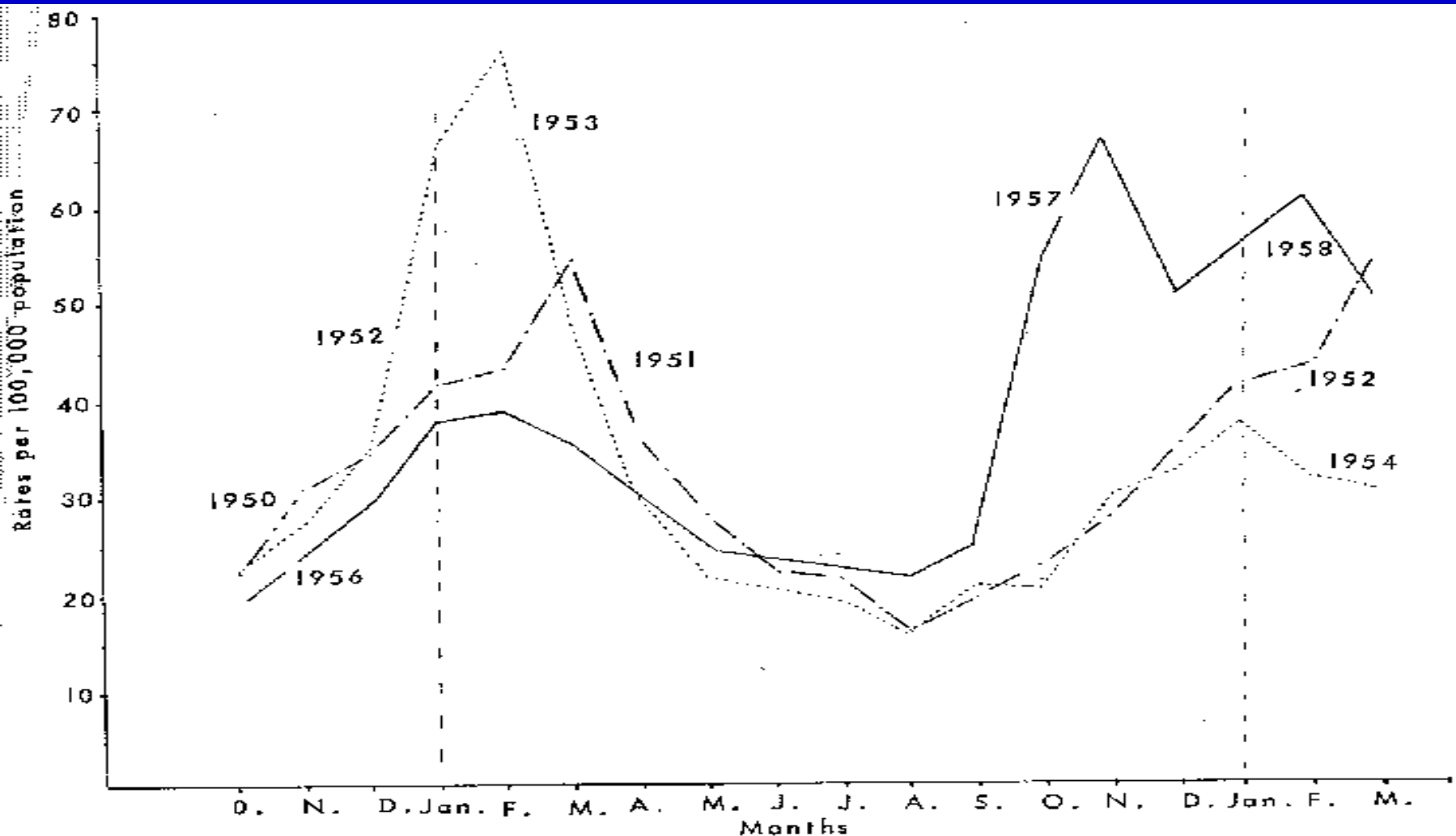"ASIAN FLU"

★ FEB-MAR 1957
■ APR-MAY 1957
■ JUN-JUL-AUG 1957

1957-58 Asian Flu (H2N2)

- **Characterized by localized outbreaks prior to explosive spread in early fall**

- **Most deaths were in older age groups**

- **Most excess deaths were categorized as cardiovascular rather than pneumonia deaths**

- **1st wave: Sept, Oct, Nov 1957**

- **2nd wave: Jan, Feb, March 1958**

Estimated P&I death rates: '51, '53, '57

Excess deaths by month: 1957-58 compared to 1956-57

Month	All causes		Cardiovascular diseases		Influenza and pneumonia	
	Number	Rate [1]	Number	Rate [1]	Number	Rate [1]
September	5,090	2.9	2,620	1.5	820	0.5
October	18,780	10.9	9,470	5.5	4,430	2.6
November	16,100	9.3	5,430	3.2	5,290	3.0
December	13,540	7.8	7,330	4.2	2,610	1.5
January	6,810	3.9	3,720	2.2	2,270	1.3
February	15,430	8.9	11,410	6.6	2,840	1.6
March	2,280	1.3	530	.3	2,000	1.2

[1] Excess number per 100,000 population.

Excess mortality by age group

Age (years)	September–December 1957		January–March 1958		Total excess per 100,000 population
	Excess number	Excess per 100,000 population	Excess number	Excess per 100,000 population	
Under 1	1,670	41.0	490	12.9	56.9
1–14	2,270	4.7	650	1.4	6.1
15–24	490	2.2	150	.7	2.9
25–34	1,410	5.9	−430	−1.8	4.1
35–44	1,416	6.2	420	1.8	8.0
45–54	3,240	16.4	2,410	12.2	28.6
55–64	7,500	50.2	3,760	25.1	75.3
65–74	15,220	156.5	6,890	70.7	227.2
75 and over	20,310	405.2	10,010	199.7	604.9

1968-69 Hong Kong Flu (H3N2)

- Widespread circulation by Dec 1968
- Same virus returned the next 3 seasons
- Elderly again most vulnerable, but a greater proportion of deaths occurred in <65, compared to 1957-58
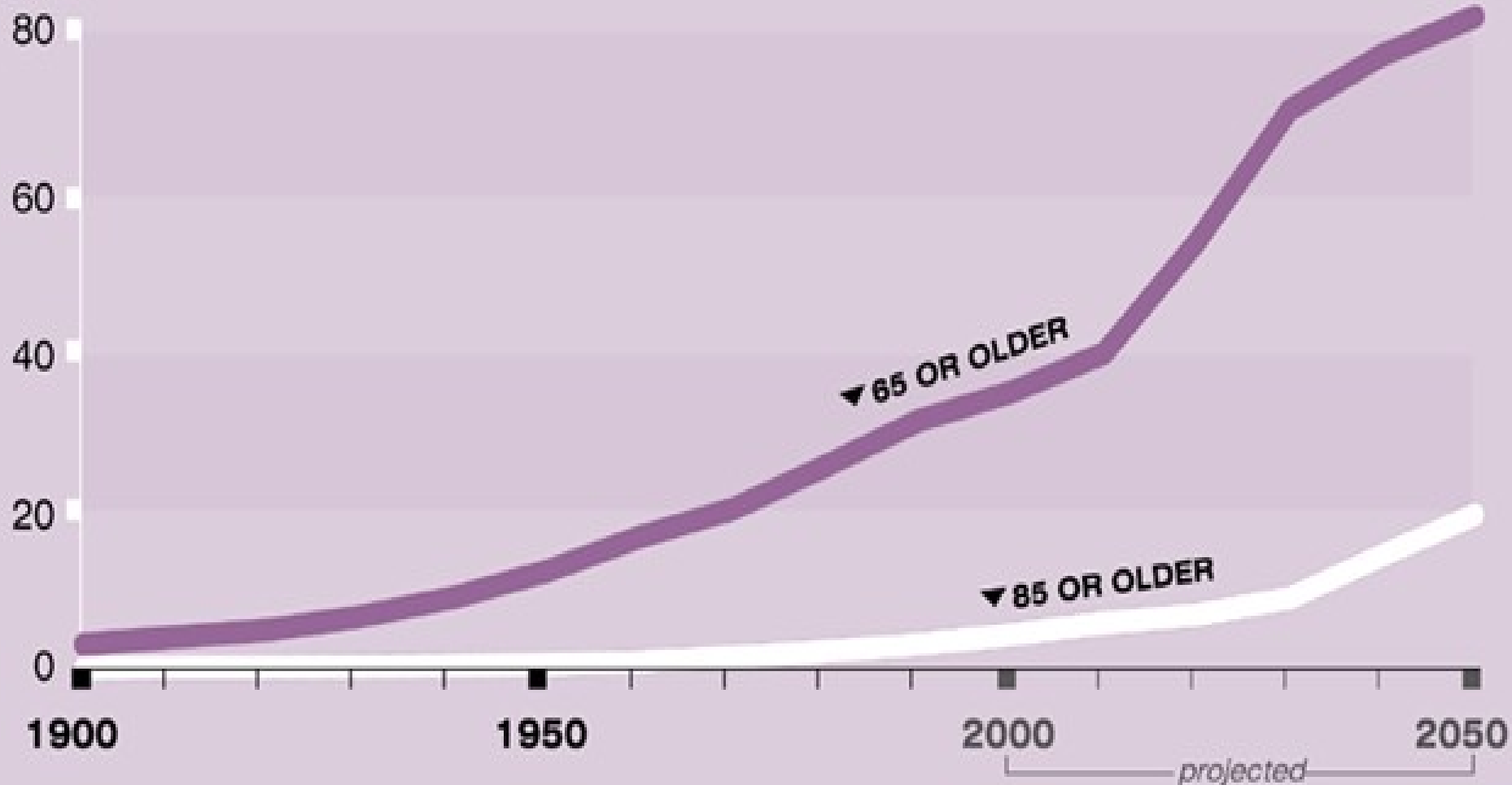- Excess deaths from Sept 1968 through March 1969: 33,800

Summary

Year	U.S. Deaths	% pop	Global deaths	% global pop
1918	660,000	0.60	20-40 M	1.3-2.5
1957	70,000	0.04		
1968	34,000	0.02		
Next: low estimate	102,086	0.04	2.0 M	0.03
Next: high estimate*	315,200	0.11	7.4 M	0.12

*Assume 35% attack rate using flu aid

Total number of persons age 65 or older, by age group, 1900 to 2050, in millions

Note: Data for the years 2000 to 2050 are middle-series projections of the population.
Reference population: These data refer to the resident population.
Source: U.S. Census Bureau, Decennial Census Data and Population Projections.

Pandemic vaccines for widespread use

- Trivalent inactivated influenza vaccines usually ready for distribution 8 months after updated strains chosen

- First waves of 20th century pandemics have typically spread to all continents in 6 months or less

Production of pandemic vaccines: J.M. Wood (Phil Trans R Soc 2001)
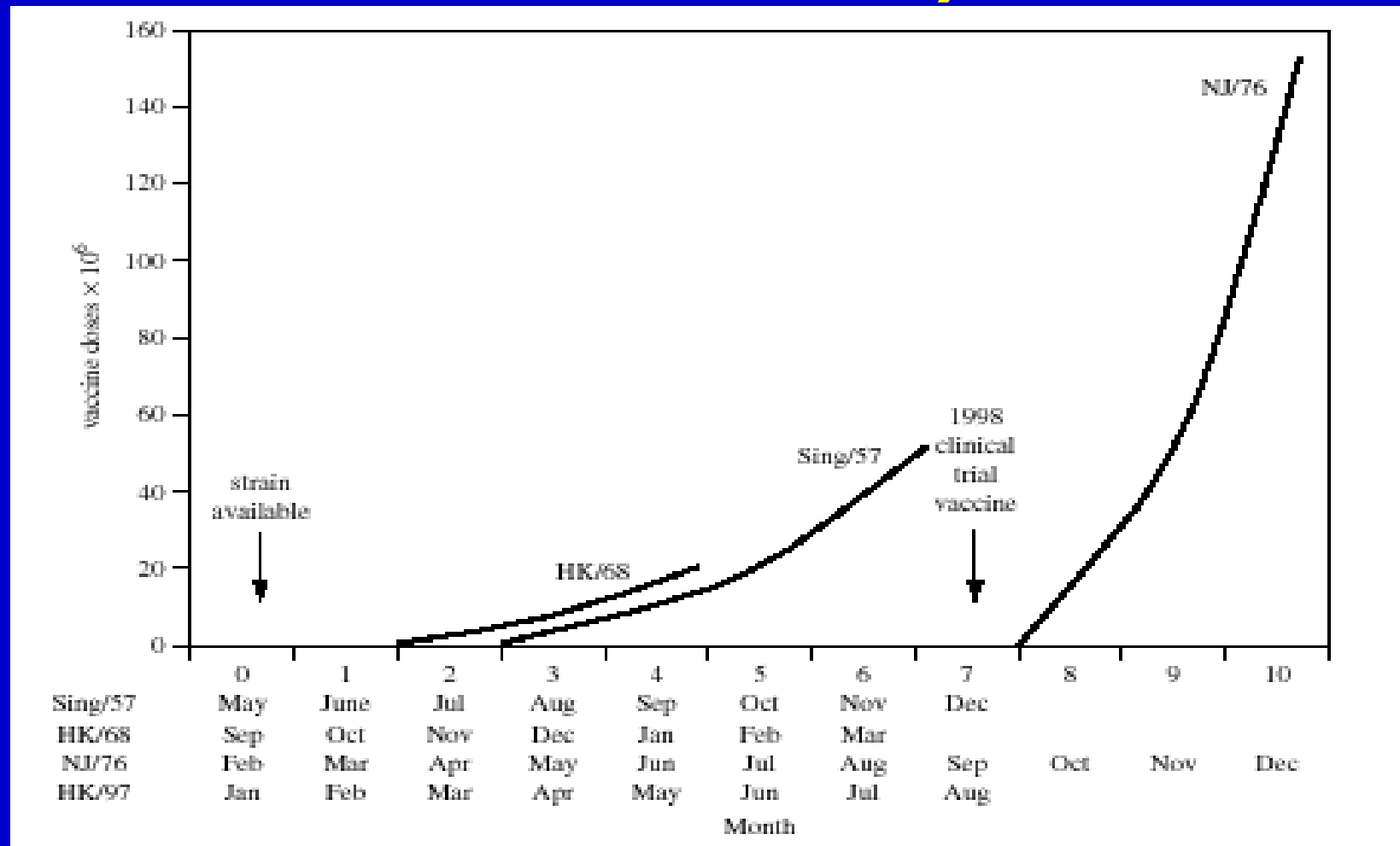
1957 A(H2N2)

- First isolates to vaccine manufacturers in May; by mid-June small amounts of inactivated, whole-cell vaccine produced

- By Aug, production at maximum of 10 M doses per month

- When 1st wave peaked in Nov, 49 M doses had been produced

1968 A(H3N2)

- Vaccine production began within 2 months of availability of new strain, improvement of ~1 month
- 1st wave peaked only 4 months from start of vaccine production
- Only 20 M doses were available

1976 A(H1N1)

- Fort Dix outbreak prompted massive effort, and high-growth reassortants available, but lead time increased to 7-8 months
- US government guaranteed purchase
- Improved vaccine purification and potency testing required additional time
- As did legislation for indemnification
- 150 M doses produced in 3 months

Future?

- Despite advances in virology and vaccine technology, the rate-limiting steps in the production and distribution of pandemic vaccines may be logistical and legal

- It seems unlikely that large amounts of vaccine will be available during the 1st pandemic wave

- Potential impacts had vaccine been available during past pandemics?

How to avoid Influenza
Gargle Daily